Formaldehyde Council

February 14, 2005

Mr. Jonathan Trout
Secretary/Treasurer
Strategic Toxic Air Reduction Program
850 Barret Avenue
Louisville, KY 40204-1745

Dear Mr. Trout:

The Formaldehyde Council, Inc. (FCI) respectfully submits comments to the Louisville Metro Air Pollution Control District (LMAPCD) on the proposed Strategic Toxic Air Reduction Program (STAR) regulation.

As outlined in detail in our comments, the FCI believes that reliance on the out-of-date EPA Integrated Risk Information System (IRIS) unit risk factor is inappropriate for numerous reasons. We recommend that LMAPCD instead follow the more recent leads of Health Canada and EPA's Office of Air which both relied instead on the CIIT model as a far more accurate benchmark for assessing risk. This approach will ensure that the information that is considered is the most current and scientifically credible.

We would be happy to meet with you in person to review any of this information.

Please contact me at 703.741.5750 should you have any questions.

Sincerely,

Betsy M. Natz

Betsy Natz
Executive Director

Enclosure

FORMALDEHYDE COUNCIL, INC.
1300 Wilson Blvd, Arlington, Virginia 22209 • 703-741-5750 • fax 703-741-5751
www.formaldehyde.org

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AIR TOXICS, FORMALDEHYDE AND RISK CHARACTERIZATION

February 2005

Introduction and Summary

A key question for all chemical substances is their proper risk characterization. Sound regulations must be founded on a solid understanding of potential risk, and regulatory agencies strive to use the best science available in their decision-making.

In the case of formaldehyde, the state of the science is robust. This paper summarizes the evolution of formaldehyde risk assessment over the past few years and supports the use of CIIT's analysis of formaldehyde risk, which is based on the best available science and most advanced application of available mechanistic and dosimetric science of the dose-response for portal of entry cancers due to formaldehyde exposures.

Lacking sufficient evidence showing cancer in exposed humans, regulators have often made predictions of cancer risk posed by low-dose exposure based on extrapolation from laboratory animal data. Estimates of the risk of developing cancer as the result of exposure to formaldehyde have been lowered over time as new experimental data have replaced default assumptions and mathematical models for extrapolating from animals to humans and high doses to low doses have become more sophisticated.

With input from the Environmental Protection Agency (EPA), Health Canada, and peer reviewers, a team of researchers at the Chemical Industry Institute of Technology (CIIT) published a thorough evaluation of potential cancer risk from formaldehyde in 1999, incorporating over 20 years of research and integrating various toxicological, mechanistic, and dosimetric data.[1] Quantitatively, CIIT predicted that cancer risk is negligible until exposures reach a level associated with cytotoxicity, which is in the range of 600 to 1,000 ppb (738 – 1230 ug/m^3).

EPA's National Center for Environmental Assessment (NCEA) currently is reconsidering its 1987 Integrated Risk Information System (IRIS) database materials for formaldehyde, but this review is not anticipated to be completed until 2007.[2] In the meantime, EPA's Office of Air and Radiation (OAR) is using an updated formaldehyde risk assessment

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[1] CIIT, *Formaldehyde: Hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation* (revised ed. 1999).

[2] In November, 2004, U.S. EPA announced its plan to await findings from an updated National Cancer Institute (NCI) study before finalizing its review of formaldehyde under the IRIS program. NCI has begun its work on the 18-month to two-year update that includes extending the mortality follow-up, updating exposure histories, and conducting a preliminary review of work histories to determine whether to undertake further quantitative exposure assessments. By updating the cohort, additional cancer deaths occurring within the cohort over the past eight (1995-2002) years are expected to nearly double the number of deaths and expected cancers in the study, thereby making risk estimates more precise (narrowing the confidence levels).

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based on the CIIT evaluation in recent rulemakings issued under the Maximum Achievable Control Technology (MACT) provisions of the federal Clean Air Act. EPA's Office of Air Quality Planning and Standards (OAQPS) has tabulated dose-response values used in the risk assessment of hazardous air pollutants, including formaldehyde.

I. The CIIT Model - A Biologically-Based Approach

With input from EPA, Health Canada, and peer reviewers, a team of researchers at the Chemical Industry Institute of Technology (CIIT) published a thorough evaluation of potential cancer risk from formaldehyde in 1999, incorporating over 20 years of research and integrating various toxicological, mechanistic, and dosimetric data.[3] Quantitatively, CIIT predicted that cancer risk is negligible until exposures reach a level associated with cytotoxicity, which is in the range of 600 to 1,000 ppb. CIIT evaluated two exposure scenarios using this model. The resulting cancer risk estimates are many orders of magnitude lower than the 1987 and 1991 EPA estimates, even though the CIIT estimation still includes many conservative assumptions. For comparison to earlier EPA values, the predicted risk at levels of 0.1 ppm (123 ug/m^3) are given below:

- *Occupational*. The first scenario assumes 40 years of occupational exposure to formaldehyde for 8 hours per day, 5 days per week, beginning at age 18. The scenario also assumes background exposure of 0.004 ppm over an 80-year lifetime. Under these conditions, at a level of 0.1 ppm (123 ug/m^3) for the occupational exposure, the model predicts the increased lifetime risk of cancer is 1.0 x 10^{-7} or 1 in 10,000,000 (ten million) for smokers and 4.1 x 10^{-9} or 4.1 in 1,000,000,000 (one billion) for non-smokers.

- *Environmental*. The second scenario assumes 80 years of continuous exposure to formaldehyde. Using this scenario, the increased risk of developing cancer from a lifetime of exposure to 0.1 ppm (123 ug/m^3) is estimated at 6.7 x 10^{-7} or 6.7 in 10,000,000 (ten million) for smokers and 2.7 x 10^{-8} or 2.7 in 100,000,000 (one hundred million) for non-smokers.

The CIIT model overcomes problems that exist in the application of "standard" risk-assessment methods, which result in incorrect projections. One situation is exemplified by chemicals, such as formaldehyde, which humans are exposed to low levels on a daily basis as part of normal cellular metabolism and for which humans are physiologically well-equipped to handle. In conducting an assessment for such a chemical, the assessor should consider, as in the case of formaldehyde, the fact that it is a normal component of metabolism, with multiple pathways existing for its conversion into a usable carbon source (*i.e.*, formate). Formaldehyde should be regarded differently, therefore, than an agent that has no role in normal physiology. This is one of the limitations in standard risk assessment that the CIIT model overcomes.

A series of twelve papers has been published using the CIIT model over the past five years. The most recent, published in July 2004, provides an analysis of human respiratory tract cancer risks of inhaled formaldehyde.[4] The paper concludes that cancer

[3] CIIT, *Formaldehyde: Hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation* (revised ed. 1999).

[4] Conolly, RB, Kimbell, JS, Janszen, D, Schlosser, PM, Kalisak, D, Preston, J and Miller, FJ. Human Respiratory Tract Cancer Risks of Inhaled Formaldehyde: Dose-Response Predictions Derived From

risks associated with inhaled formaldehyde are *de minimis* (10^{-6} or less) at relevant human exposure levels, and protection from the non-cancer effects of formaldehyde should be sufficient to protect from its potential carcinogenic effects.

The CIIT model also displays calculations using the modern-day default method of a benchmark dose model. The EPA draft guidelines for cancer risk assessments issued in 1996 included the benchmark dose model for use when biology and toxicology data are not available to develop a more sophisticated biologically-based dose-response model such as the clonal growth model for formaldehyde. The benchmark dose analysis uses a statistical curve-fitting approach to fit experimental data. Using benchmark dose modeling and different sets of experimental data, CIIT calculated lifetime cancer risk estimates from exposure to 0.1 ppm of formaldehyde at 3.9 - 4.2 x 10^{-4}. This is only slightly less stringent than the default linear extrapolation approach. This again illustrates the conservatism of the default approaches compared to a biologically-based approach incorporating more data in lieu of assumptions.[5]

II. Peer Review of the CIIT Report

During its development, the CIIT Report underwent extensive review by EPA, Health Canada, and other peer reviewers. EPA and Health Canada representatives participated regularly in advising CIIT and reviewing the work throughout the development of the CIIT Report. Dr. John Overton (in EPA's National Health and Environmental Effects Research Laboratory) prepared two sections, "Human Respiratory Tract Dosimetry for Formaldehyde," and "Mathematical Model for Mass Transport." EPA's Dr. Vanessa Vu and Annie Jarabek provided advice to CIIT, as did Bette Meek of Health Canada. EPA and Health Canada sponsored a peer review workshop on the draft version of the CIIT Report in 1998.[6] Several EPA and Health Canada staff members attended and participated in this workshop, and their comments were incorporated into the final version of the CIIT Report. The Workshop reviewers unanimously agreed that the model provided in the CIIT Report "offers considerable improvement over the default methodology adopted in previous assessments."[7] Further,

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Biologically-Motivated Computational Modeling of a Combined Rodent and Human Dataset, *ToxSci* Advance Access *at* http://www.toxsci.oupjournals.org (2004).

[5] In June 2004, the International Agency for Research on Cancer (IARC) changed its hazard classification for formaldehyde from a "probable" to a "known" human carcinogen. The IARC reclassification does not undermine the CIIT analysis for several reasons. First, in contrast to CIIT's complete risk assessment approach, the IARC classification is a 'hazard identification,' the first of several steps in the risk assessment process. IARC simply tries to answer the question of whether, under any circumstances, a substance could produce cancer in humans. The IARC reclassification is not a finding of actual risk or that workers and the public are *actually* at risk at current exposure levels. Second, and perhaps even more importantly, the IARC decision was based on the results primarily on a single study: Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair, A. *Mortality from lymphohematopoietic malignancies among workers employed in formaldehyde industries*. J Natl Cancer Inst 2003; 95: 1615–23 (NCI study). The trend observed in the NCI study was based on very small numbers for a rare cancer: 8 observed and 4 expected among exposed, and the excess risk was limited to a single plant, which itself suggests that confounding factors may be at issue. Because of the inherent uncertainties, NCI has agreed to update the study, as was noted in Footnote 2, above. We anticipate that the NCI update will greatly strengthen the study's statistical validity and significance, which is why EPA is deferring its IRIS update. In any event, the CIIT risk assessment remains the best model for projecting potential human risk.

[6] For more information see Report of Health Canada/U.S. EPA External Peer Review on Formaldehyde, Ottawa, Ontario (March 18-20, 1998).

[7] *Id.* at 4.

once the refinements suggested by the review group were incorporated, the peer reviewers "strongly endorsed" the use of the CIIT model, noting that the model provides "the opportunity to use a broader database for risk assessment for formaldehyde and should reduce the overall uncertainty."[8]

III. EPA OAQPS Use of the CIIT Model

EPA's Office of Air Quality Planning and Standards (OAQPS) has tabulated dose-response values used in the risk assessment of hazardous air pollutants.[9] OAQPS uses the CIIT analysis in its chronic inhalation risk assessment of exposure to formaldehyde, which is 5.5 $\mu g/m^3 \times 10^{-9}$.[10] Based on this unit risk factor, the benchmark ambient concentration for formaldehyde, a concentration representative of an additional lifetime cancer risk of 1 in 1,000,000 ($1 \times 10E^{-6}$) is 0.149 ppm (183 ug/m^3). This updated estimate of chronic inhalation risk, based on the CIIT risk assessment, has been used by the EPA Office of Air and Radiation (OAR) in the development of two rules issued under the Maximum Achievable Control Technology (MACT) provisions of the federal Clean Air Act. These include MACT rules for plywood and composite wood products and combustion turbines. In fact, OAR specifically states the following in the preambles to those rulemakings:

> "For formaldehyde, we do not use the dose-response value reported in IRIS. The dose-response value in IRIS is based on a 1987 study, and *no longer represents the best available science* in the peer-reviewed literature. Since that time, significant new data and analysis have become available."[11]

> "We based the dose-response value we used for formaldehyde on work conducted by the CIIT . . . The risk assessment analyzed carcinogenic risk from inhaled formaldehyde using approaches that are consistent with EPA's draft guidelines for carcinogenic risk assessment."[12]

> "We believe that the CIIT modeling effort represents the best available application of the available mechanistic and dosimetric science on the dose-response for portal of entry cancers due to formaldehyde exposures . . . The CIIT model incorporates

[8] *Id*.

[9] They are available at http://www.epa.gov/ttn/atw/toxsource/summary.html.

[10] According to OAQPS, "[a] new EPA IRIS assessment is underway in light of a CIIT analysis that supports a URE on the order of 5.5E-9 per $\mu g/m^3$. This value is substantially lower than the current IRIS URE of 1.3E-5 per $\mu g/m^3$." Adjustments and Special Cases for Chronic Inhalation Risk Assessment (April 29, 2004), available at http://www.epa.gov/ttn/atw/toxsource/adjustments.html.

[11] 69 Fed. Reg. 18333 (Apr. 7, 2004) (emphasis added). The 1987 U.S. EPA calculation of the increased risk of developing cancer from a 70-year lifetime of exposure to 0.1 ppm of formaldehyde was 1.6 x 10-3 or 1.6 in 1,000. This calculation was based on a default assumption that the dose-response curve would be linear at doses all the way down to zero. In 1991, the U.S. EPA reevaluated its risk assessment for formaldehyde and calculated (but never finalized) two values for the increased risk of developing cancer from a lifetime of exposure to formaldehyde. The first estimate, based on experimental data from studies with rats, was a risk of 2.8 x 10-4 or 2.8 in 10,000 over a lifetime for exposure to 0.1 ppm. This is about 6 times lower than the 1987 estimate. The second estimate, based on experimental data from studies with monkeys, was 3.3 x 10-5 or 3.3 in 100,000 at 0.1 ppm. This is about 50 times lower than the 1987 estimate. These estimates were based on a default linear risk estimation procedure but incorporated information on delivered dose.

[12] 69 Fed. Reg. 18333 (Apr. 7, 2004).

state-of-the-art analysis for species-specific dosimetry, and encompasses more of the available biological data than any other currently available model."[13]

IV. International Recognition of the CIIT Approach

In addition, several international groups have updated their characterizations of formaldehyde to state that formaldehyde is likely to be carcinogenic in humans only at doses that cause cell proliferation, and not at low doses. These widely respected organizations drew heavily on the CIIT approach.

- In its review of formaldehyde under its Existing Chemicals program, the Organization for Economic Cooperation and Development (OECD) issued a Screening Information Data Set (SIDS) Initial Assessment Report, which stated, "The increasing severity of damage in higher concentrations is a function of the concentration. Another way of expressing this result is that formaldehyde toxicity is independent of the total dose (c x t) but that it depends on the dose rate [(c x t)/t = c] or concentration. This can be explained by saturation of detoxification pathways for formaldehyde at high concentrations. Strong non-linearity in the induction of cell proliferation, DNA-protein-crosslinks, cytotoxic effects and carcinogenicity are observed (CIIT 1999). The observed non-linearity is likely attributable to a large extent to mechanisms present in biological systems to deal with low levels of formaldehyde."[14] In sum, the report found that "[t]aking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions."[15] OECD found no further research on human health was needed.

- In an updated assessment of formaldehyde, Health Canada stated that it considered the CIIT dose-response model "to provide the most defensible estimates of cancer risk, on the basis that it encompasses more of the available biological data, thereby offering considerable improvement over default."[16]

- In finalizing the Concise International Chemical Assessment Document on Formaldehyde,[17] in March 2002, the World Health Organization relied on the CIIT cancer risk assessment for formaldehyde and concluded that formaldehyde exposure poses a carcinogenic hazard only under conditions that both induce toxicity and cause sustained regenerative proliferation.

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[13] 69 Fed. Reg. 18333-34 (Apr. 7, 2004) (emphasis added). As has been common for EPA MACT rules, EPA's plywood MACT rule was the subject of a judicial petition for review. *NRDC and Sierra Club v. U.S. EPA*, Case No. 04-1323 (D.C. Cir.). NRDC also filed a petition for reconsideration directly with EPA. EPA is currently assessing the merits of the petition for reconsideration it received and is projected to act on the petition by mid-2005. In the interim, the judicial proceedings have been stayed.

[14] Organization for Economic Cooperation and Development (OECD), SIDS Initial Assessment Profile, at 18.

[15] SIDS Initial Assessment Profile, at 2.

[16] Environment Canada and Health Canada, Existing Substances Evaluation, Assessment Report -- Formaldehyde, at 68 (2002), *at* http://www.ec.gc.ca/substances/ese/eng/psap/final/formaldehyde.cfm .

[17] The CICAD is *available at* http://www.inchem.org/documents/cicads/cicads/cicad40.htm.

- The German MAK Commission, which sets occupational exposure values, reviewed formaldehyde and concluded: "In the low dose range, which does not lead to an increase in cell proliferation, the Commission therefore considers that the genotoxicity of formaldehyde plays no or at most a minor part in its carcinogenic potential so that no significant contribution to human cancer risk is expected."[18] This conclusion is supported by the results of a risk assessment which, for persons exposed to concentrations of 0.3 ml/m^3 (0.37 mg/m^3) at the workplace for 40 years, yielded a very low additional cancer risk for non-smokers of 1.3 x 10^{-8} and for smokers of 3.8 x 10^{-7} (CIIT 1999).[19]

V. At Present, It Would Be Inappropriate for Regulatory Authorities to Rely on the IRIS Health Benchmarks for Formaldehyde

As described by EPA, the IRIS "database includes chemical specific summaries of qualitative and quantitative health information in support of the first two steps of the risk assessment process, *i.e.*, hazard identification and dose-response evaluation. Combined with specific situational exposure assessment information, the information in IRIS may be used as a source in evaluating potential public health risks from environmental contaminants."[20]

While the IRIS database can be a useful tool for obtaining information about the health effects of individual chemicals, it is a non-statutory, in-house Agency activity. IRIS data base entries are not subject to the safeguards associated with formal rulemaking. Not surprisingly, EPA management has repeatedly emphasized that the Agency is required to consider other information, in addition to the IRIS database, when evaluating the health effects of chemicals in a regulatory context.[21]

In guidance on the use of IRIS for purposes of developing values under the early reduction program of the Clean Air Act, EPA noted:

> It is also important to remember that IRIS is not a comprehensive toxicological database. There may be more recent, credible and relevant information available than is contained in IRIS. Moreover, the act of including a value in IRIS is not subject to notice and comment rulemaking, and may not necessarily have been subjected to external peer review . . . . Accordingly, IRIS values are not entitled to conclusive weight and shall not be made legally binding in the context of any other rulemaking action. In addition, EPA or any State agency that uses IRIS should not rely exclusively on IRIS values but should consider all credible and relevant information that is submitted in any particular rulemaking. If an outside party questions IRIS values during the course of an

[18] German MAK Commission, Formaldehyde (Official English Translation), at 193 (3001).

[19] MAK Commission on Formaldehyde, at 193.

[20] 69 Fed. Reg. 5971 (Feb. 9, 2004).

[21] *See Community Nutrition Instit. v. Young*, 818 F.2d 943, 946 (D.C. Circuit 1987), *McLouth Steel Prods. Corp. v. EPA*, 838 F.2d 1317 (D.C. Cir. 1988).

> EPA proceeding. . . , EPA will consider all credible and relevant information before it in that proceeding.[22]

These statements were intended to avoid inflexible adherence to values found in the IRIS database, without regard to when they were derived or how well they conform to current EPA practices. EPA's Office of Air Quality Planning and Standards (OAQPS) Directive states unequivocally:

> It is important to remember, however, that the IRIS data base is only a starting point for risk assessments. The IRIS data base is not meant to replace careful thought and analysis necessary for doing a risk assessment . . . .
>
> Accordingly, IRIS values are not entitled to conclusive weight and shall not be made legally binding in the context of any other rulemaking action. In addition, EPA or any State agency that uses IRIS should not rely exclusively on IRIS values but should consider all credible and relevant information that is submitted in any particular rulemaking.[23]

The same points were made in an EPA Office of Solid Waste and Emergency Response (OSWER) Directive, which states:

> IRIS is not the only source of toxicological information, and in some cases more recent, credible and relevant data may come to the Agency's attention. . . . Such information should be considered along with the data in IRIS in selecting toxicological values; ultimately, the Agency should evaluate risk based on its best scientific judgment and consider all credible and relevant information available to it.[24]

The OSWER Directive states further that "entry of a value on IRIS does not make the number legally binding (*i.e.*, the value is not entitled to conclusive weight)."[25] The policy embodied in these directives were affirmed by EPA Administrator Whitman, who stated:

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[22] U.S. EPA, Office of Air Quality Planning and Standards, Guidance on the Use of Integrated Risk Information System (Aug. 26, 1994).

[23] OAQPS Directive at 2.

[24] EPA OSWER Directive No. 9285.7-16 (Dec. 21, 1993)(Use of IRIS Values in Superfund Risk Assessment). EPA also noted that:

> [T]he Agency must respond substantively to any comments raised during the public comment period on the proposed plan that question the use of an IRIS value; *see* 55 FR 8711 (March 8, 1990). In responding to such comments, Agency staff should keep in mind that the entry of a value in IRIS is not a rulemaking. Thus, the entry of the value on IRIS does not make the number legally binding (*i.e.*, the value is not entitled to conclusive weight) for the purposes of Superfund risk assessments. When a toxicological value is questioned in a comment on the proposed plan, a written explanation for the value ultimately selected (whether it is the IRIS value or another number) must be included in the administrative record [footnote omitted].

[25] *Id.*

> EPA recognizes that IRIS is not a comprehensive toxicological database. There may be more recent relevant information available than is contained in IRIS. IRIS values are not rules adopted after notice and comment rulemaking, although recent IRIS assessments are posted on the Internet and public comments are solicited. IRIS values are not legally binding and are not entitled to conclusive weight in any rulemaking. In addition, EPA or any State agency that uses IRIS should not rely exclusively on IRIS values but should consider all credible and relevant information that is submitted in any particular rulemaking.[26]

EPA's statements are clear. When evaluating chemicals in a regulatory context, EPA must use a scientifically appropriate health benchmark, and when determining that health benchmark, must consider all relevant information to ensure that the health benchmark is up-to-date and scientifically credible – even if that means departing from the value in IRIS. Obviously, the same is true for other regulatory agencies.

VI. Conclusion

For the reasons stated above, it would be inappropriate for any agency to rely on the 1987 EPA IRIS unit risk factor in establishing a property line concentration threshold for formaldehyde.

Based on its use by U.S. EPA and broad global acceptance, air toxic and other regulatory analyses of formaldehyde's toxicological significance should be based on the CIIT model. As a result, one would conclude that formaldehyde exposures at or below 0.6 ppm (738 ug/m^3) pose less than one in a million risk of respiratory tract cancer and, therefore, are properly considered *de minimis.*

[26] 66 Fed. Reg. 46928, 46929 (Sept. 7, 2001) (reflecting settlement of legal action brought under the Safe Drinking Water Act).